

122

IPN

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## WO9919300A1: PROSTAGLANDIN AGONISTS AND THEIR USE TO TREAT BONE DISORDERS

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**Premium Data** <sup>1</sup>: [More choices...](#)

**Inventor(s):** CAMERON, Kimberly, O'Keefe , 5 North Winchester Court, East Lyme, CT 06333, United States of America  
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**Applicant(s):** PFIZER INC., 235 East 42nd Street, New York, NY 10017, United States of America

**Issued/Filed Dates:** April 22, 1999 / Oct. 5, 1998

**Application Number:** WO1998IB0001540

**IPC Class:** C07D 213/71; C07C 311/13; C07D 401/12; C07D 405/12; C07D 409/12; C07D 417/12; C07D 233/84; C07D 403/12; A61K 031/18; A61K 031/40; A61K 031/415; A61K 031/435; A61K 031/425; A61K 031/505;

**Designated Countries:** AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, **European patent:** AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, **OAPI patent:** BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG, **ARIPO patent:** GH, GM, KE, LS, MW, SD, SZ, UG, ZW, **Eurasian patent:** AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

**Abstract:** This invention relates to prostaglandin agonists, methods of using such prostaglandin agonists, pharmaceutical compositions containing such prostaglandin agonists and kits containing such prostaglandin agonists. The prostaglandin agonists are useful for the treatment of bone disorders including osteoporosis.

[\[Show "fr" Abstract\]](#)

**Attorney, Agent, or Firm:** SPIEGEL, Allen, J.;  
**Foreign References:** none

(No patents reference this one)



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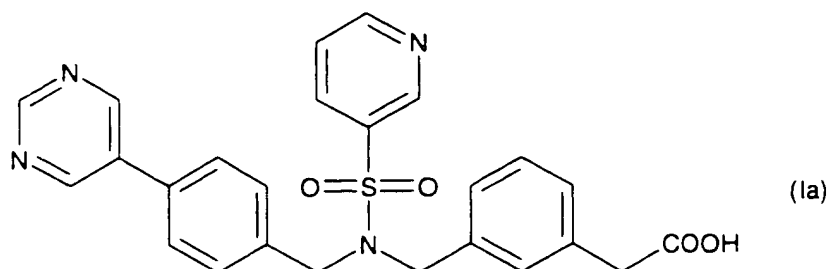
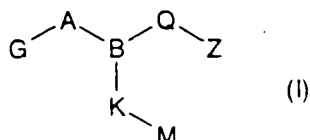
SEARCH PATENT FULL TEXT WITH NATURAL LANGUAGE

New prostaglandin agonists - useful for the treatment of bone diseases (e.g. osteoporosis), kidney degeneration and glaucoma.

**Drug Activity:** Osteopathic; Antiinflammatory; Nephrotropic; Ophthalmological; Hypotensive

**Mechanism of Action:** Prostaglandin-Agonist

**Compound Name:** None Given



**Use:** For the treatment of osteoporosis (e.g. glucocorticoid-induced osteoporosis), osteotomy, childhood idiopathic bone loss or bone loss associated with periodontitis; for augmenting and maintaining bone mass (e.g. following facial reconstruction or treating bone fracture); for treating kidney degeneration, glaucoma, ocular hypertension (claimed) and as prostaglandin agonists.

**Dosage:** 0.001-100 (0.01-10) mg/kg/day. Administration may be systemic or local, such as oral, parenteral and intraduodenal.

**Advantage:** None given.

**Biological Data:** No data given.

**Chemistry:** Compounds of formula (I) and their prodrugs and salts are new.

A = SO<sub>2</sub> or CO; G = a defined aryl or bi-aryl containing group, arylamino, or R<sub>1</sub>R<sub>2</sub>-amino.

R<sub>1</sub>, R<sub>2</sub> = H or alkyl, or together NR<sub>1</sub>R<sub>2</sub> is a 5/6-membered heterocycle; B = N, or CH; Q = a defined divalent linking group such as alkylene optionally substituted and optionally interrupted by an aromatic ring.

Z = carboxyl, alkoxycarbonyl, tetrazolyl, 1,2,4-oxadiazolyl, 5-oxo-1,2,4-oxadiazolyl, 5-oxo-1,2,4-thiadiazolyl, alkylsulfonylcarbonyl, or phenylsulfonylcarbonyl; K = a bond, or alkylene optionally substituted and optionally interrupted by O or S; M = defined aryl, or defined biaryl (in which the aryl groups are linked via a heteroatom, a divalent linking group (e.g. alkylene) or directly by a bond); Provisos are given.

Several compounds are specifically claimed e.g. (3-(((pyridine-3-sulfonyl)-(4-pyrimidin-5-yl-benzyl)-amino)-methyl)-phenyl)-acetic acid (1a) (example 1a).

249 pages

Drawings 0/0

**Authors:** Cameron K O; Lefker B A; Rosati R L

**Publication Date:** 22 April 1999

**Language:** English

**Priority:** 10 October 1997 US-061727

**Location:** New York, N.Y., USA

**Document Number:** WO9919300-A1

**Filed:** 05 October 1998 as IB1540

**Designated States:** Regional: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE (ARIPO) (Eurasian) (OAPI) National: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW

EP911321

Pfizer

Prostaglandin agonists used in the treatment of osteoporosis. See WO9827976 and WO9828264.

(11) EP 0 911 321 A2

EUROPEAN PATENT APPLICATION

(43) Date of publication: 28 Oct 1999 Bulletin 1999/17

(71) Applicant: Pfizer Inc., New York, NY, USA

(72) Inventor: Carolyn R. Sanders, New York, NY, USA

(54) Designated Contracting States: AT BE CH CY DE DK ES FR GB GR IT LI LU MC NL PT SE

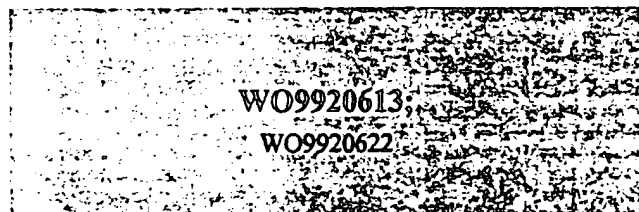
(57) The invention relates to prostaglandin agonists used in the treatment of osteoporosis.

Structure is taken from Page 3 of the specification

Chemical structure: R1-C(=O)-Z-C(R2)(R3)-R4

EP 0 911 321 A2

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Pierre Fabre

1-4 Difunctionalised cyclohexane and 3-oxo-2(H)-1,2,4-triazine derivatives as 5-HT<sub>1A</sub> receptor ligands. Related to compounds claimed by Patoiseau and Dupont-Passelaigue in WO9501965 and WO9616949.

(11) WO 99/20613

(12) International Patent Classification: C07D 333/00, A61K 31/00, C07D 409/12, C23/12

(13) International Filing Date: 14 October 1998

(14) Language of original text: English

(15) Applicant: PIERRE FABRE MEDICAMENT (FR) 45, place Adam-Garcin, F-62100 Boulogne-sur-Mer (FR)

(16) Inventor(s): PATOISEAU Jean-François (FR) 7, rue Jules Ferry, F-41100 Cadenet (FR); DUPONT-PASSELAIGUE Etienne (FR) 22, rue du Commerce, F-41100 Cadenet (FR); ROZE R. Vincent (FR) 1, rue de la République, F-41100 Cadenet (FR); MARTIN Jean-Jacques (FR) 28, avenue Robespierre, F-75116 Paris (FR)

(17) Designated States: AU BR CA CN JP MA MX EP (A) DE CH CY DK ES FR GB GR IT LI LU MC NL PT SE

(18) The CYCLOHEXANE DERIVATIVES OF FUNCTIONALIZED BY 1,4 AS LIGANDS OF 5-HT<sub>1A</sub> RECEPTORS

(19) The invention relates to cyclohexane derivatives of functionalized by 1,4 as ligands of 5-HT<sub>1A</sub> receptors. The invention also relates to the use of compounds of general formula (I) with pharmacological activity in the treatment of various diseases.

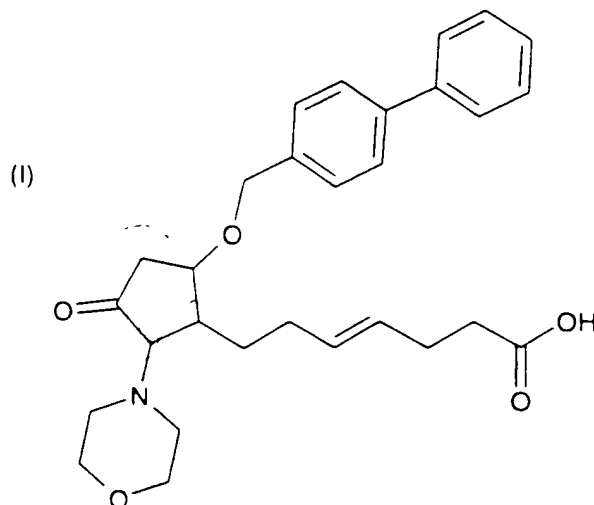
Chemical structures: (I) C1CCC(CC1)C(=O)R, (II) C1CCC(CC1)C(=O)R, (III) C1CCC(CC1)C(=O)R, (IV) C1CCC(CC1)C(=O)R, (V) C1CCC(CC1)C(=O)R, (VI) C1CCC(CC1)C(=O)R

Use of EP4 receptor antagonists as bone resorption inhibitors - for the treatment of osteoarthritis, rheumatoid arthritis, osteoporosis, inflammatory bone diseases and hypocalcemia.

**Drug Activity:** Osteopathic; Antiarthritic; Antirheumatic; Antiinflammatory; Cardiovascular-Gen.

**Mechanism of Action:** Prostaglandin-Antagonist-EP4; Prostaglandin-Antagonist-E2

**Compound Name:** None Given



**Use:** As EP4 antagonists for the treatment of conditions with accelerated bone resorption (claimed) e.g. osteoarthritis, rheumatoid arthritis, osteoporosis, inflammatory bone diseases and hypocalcemia.

**Dosage:** 0.1-200 (0.1-10) mg/kg/day. Administration may be oral, parenteral, rectal or by inhalation.

**Advantage:** The compounds prevent accelerated bone resorption by inhibiting PGE<sub>2</sub>-stimulated osteoclast-like cell formation in bone marrow.

**Biological Data:** None given.

**Chemistry:** The use of an EP4 antagonist in the treatment of conditions with accelerated bone resorption is claimed.

Preferably the EP4 antagonist is [1 $\alpha$ (Z),2 $\beta$ ,5 $\alpha$ ]-(-)-7-[5-[(1,1'-biphenyl)-4-yl]methoxy]-2-(4-morpholinyl)-3-oxocyclopentyl]-4-heptenoic acid (I) or its [1R[1 $\alpha$ (Z),2 $\beta$ ,5 $\alpha$ ]]-(-)-isomer or their salts and solvates.

7 pages

Drawings 0/0

**Authors:** Foord S M; Sheldrick R L G; Lumley P

**Publication Date:** 21 April 1999

**Language:** English

**Priority:** 07 February 1998 GB-002599

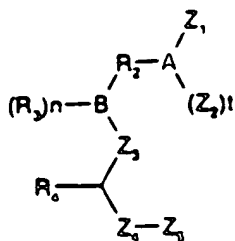
**Location:** Greenford, U.K.

**Document Number:** GB2330307-A

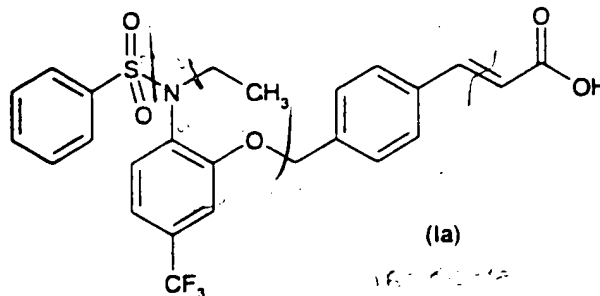
**Filed:** 07 February 1998 as 002599

New sulfonamide and carbamate derivatives bind to prostaglandin E2 receptors - useful for e.g. promoting and inhibiting digestive tract motility, causing analgesia and as hypotensives.

**Drug Activity:** Inotropic-Pos.; Inotropic-Neg.; Gynecological; Gastrointestinal-Gen.; Analgesic; Sedative; Vasotropic; Hypotensive; Diuretic; Antidiarrheic; Antidiabetic; Antiulcer; Antiinflammatory; Tocolytic; Laxative; Tranquilizer  
**Mechanism of Action:** Prostaglandin-Agonist-E2; Prostaglandin-Antagonist-E2  
**Compound Name:** None Given



(I)



(Ia)

**Use:** As antagonists and agonists of prostaglandin E2 (PGE2) receptors for promoting or inhibiting uterine muscle contraction or digestive tract movement, as analgesics or hypnotics, for enlarging vascular capacity, for suppressing gastric acid secretion, and as hypotensives or diuretics, for treating diarrhea, diabetes, gastric ulcers, gastritis, to aid sleep and as antenarabuficient, laxatives and tranquilizers.

**Dosage:** 1 µg-100 mg/day orally or 0.1 µg-10 mg/day parenterally.

**Advantage:** None given.

**Biological Data:** In a PGE2 receptor binding assay (Ia) had a Ki of 0.0002 µM.

**Chemistry:** Sulfonamide and carbamate derivatives of formula (I) and their salts are new.

ring A, ring B = 5-15C carbocyclyl or 5-7 membered heterocyclyl containing 1 or 2 O, N or S; Z1 = COR1, 1-4C alkylene-COR1, CH=CHCOR1, C=CCOR1, O-1-3C alkylene-COR1, or 1-5C alkylene-OH; R1 = OH 1-4C alkoxy or optionally substituted NH2; Z2 = H, 1-4C alkyl, 1-4C alkoxy, NO2, halo, CF3, CF3O, OH or COR1; Z3 = bond or 1-4C alkylene; Z4 = SO2 or CO; Z5 = 1-8C alkyl, 2-8C alkenyl, 2-8C alkynyl, optionally substituted cycloalkyl, phenyl or heterocyclyl or substituted alkyl, alkenyl or alkynyl; R2 = O, S, CO, or optionally substituted imino, CONH, NHCO or alkylene; R3 = H, 1-6C alkyl, 1-6C alkoxy, 1-6C alkythio, NO2, halo, CF3, CF3O, OH or CH2OH; R4 = H, 2-8C alkenyl, 2-8C alkynyl or optionally substituted alkyl; a, t = 1-4; provided that when A = a benzene ring and (Z2)t = COR1 then Z1 is bonded to the 3 or 4 position of A.

(I) is e.g. 4-[2-(N-ethylphenylsulphonylamino)-5-trifluoromethylphenoxyethyl] cinnamic acid (Ia).

305 pages

Drawings 0/0

Address: Chuchida S; Nagao Y

Publication Date: 25 June 1998

Language: Japanese

Priority: 21 October 1997 JP-305055

Location: Osaka, Japan

Document Number: WO9827053-A1

Filed: 12 December 1997 as J04593

Designated States: Regional: AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE Natl: AU CA CN HU JP KR MX NO US

WD-98-008828

PP - Gastrointestinal, Inflammation & Allergy

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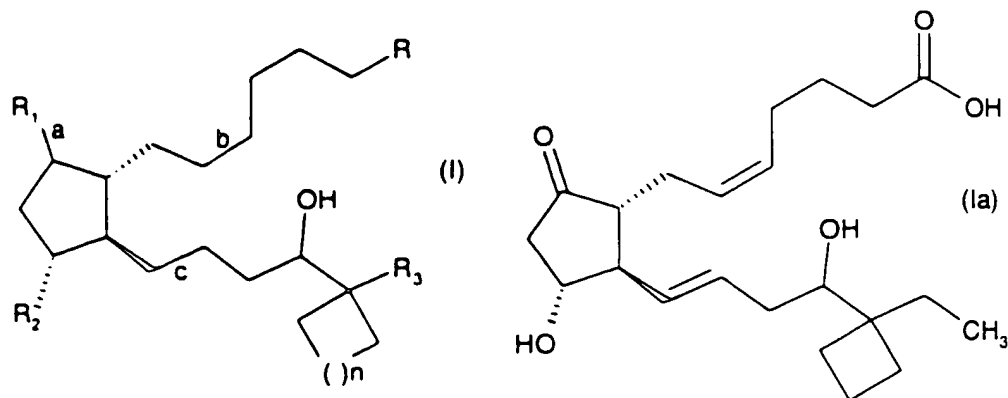
TX / 1121

New  $\omega$ -cycloalkylprostaglandin E2 derivatives are EP2 receptor modulators - useful for the treatment of e.g. immunological diseases, asthma and abnormal bone formation.

**Drug Activity:** Immunomodulator; Antiasthmatic; Osteopathic; Neuroprotective; Hepatotropic; Antiinfertility; Tocolytic; Ophthalmological

**Mechanism of Action:** Prostaglandin-Antagonist-EP2; Prostaglandin-Agonist-EP2

**Compound Name:** None Given



**Use:** As EP2 receptor modulators and for the treatment and prevention of immunological diseases, asthma, abnormal bone formation, neuronal cell death, liver damage, abortion, premature birth or retina neuropathy of glaucoma (claimed).

**Dosage:** 1  $\mu$ g-100 mg orally; 0.1  $\mu$ g-10 mg parenterally. Administration is also rectal.

**Advantage:** Improved specificity and reduced side effects.

**Biological Data:** Compounds of the invention were assayed for activity against prostanoid receptor subtypes. Compound (1a) showed  $K_i$  values of  $> 10$ , 0.030,  $> 10$  and  $> 10 \mu$ M for receptors EP1, EP2, EP3 $\alpha$  and EP4 respectively.

**Chemistry:**  $\omega$ -Cycloalkyl-prostaglandin E2 derivatives of formula (I) and their salts and cyclodextrin clathrates are new.

R = COOH or CH<sub>2</sub>OH; R<sub>1</sub> = oxo, CH<sub>2</sub> or halo; R<sub>3</sub> = alkyl, alkenyl, alkynyl (all optionally substituted) or H; n = 0-4; a = optional double bond; b = optional double or triple bond; c = optional single, double or triple bond; Provisos are given.

Several compounds are specifically claimed e.g. (5Z,11 $\alpha$ ,13E)-11,16-dihydroxy-9-oxo-17,17-propano-20-norprosta-5,13-dienoic acid (1a) (example 4(10)).

121 pages

Drawings 0/0

**Authors:** Tani K; Ohuchida S

**Publication Date:** 26 August 1998

**Language:** English

**Priority:** 06 November 1997 JP-319169

**Location:** Osaka, Japan

**Document Number:** EP-860430-A2

**Filed:** 03 February 1998 as 300769

**Designated States:** AT BE CH DE DK ES FR GB GR IE  
IT LI LU MC NL PT SE

WD-98-010805

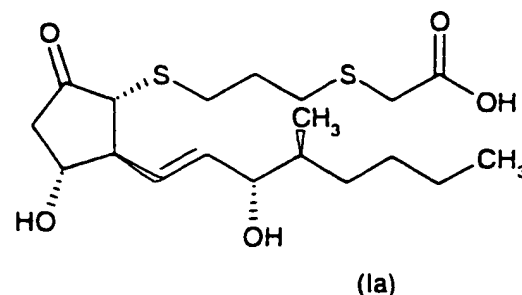
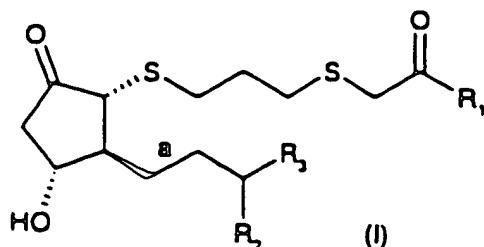
PP - Gastrointestinal, Inflammation & Allergy

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New 3,7-dithiaprostanoid acid derivatives - useful for the treatment and prevention of e.g. immunological disease, asthma, abnormal bone formation and neuronal cell death.

**Drug Activity:** Immunosuppressive; Immunostimulant; Antiasthmatic; Osteopathic; Neuroprotective; Hepatotropic; Nephrotropic; Antiinflammatory; Hypotensive; Cardiant; Vasotropic  
**Mechanism of Action:** Prostaglandin-Agonist-E2; Prostaglandin-Agonist-EP4  
**Compound Name:** None Given



**Use:** For the treatment and prevention of immunological diseases e.g. autoimmune diseases, immunological deficiency diseases and organ transplantation, asthma, abnormal bone formation, neuronal cell death, liver damage, nephritis, hypertension and myocardial ischemia (claimed).

**Dosage:** 1 µg-100 mg orally up to several times per day; 0.1 µg-10 mg parenterally up to several times per day. Administration may also be topical, rectal or vaginal.

**Advantage:** None given.

**Biological Data:** Membrane fraction was prepared using the prostanoid receptor subtypes (mouse EP3α, EP4) expressing CHO cells. A standard assay mixture containing membrane fraction (0.5 mg/ml), 2.5 nM of <sup>3</sup>H-PGE<sub>2</sub> and various concentrations of the test compounds was incubated for 1 hour at room temperature. The reaction was terminated by the addition of ice-cold buffer. K<sub>d</sub> and B<sub>max</sub> values were determined and non-specific binding was calculated as the bound in the presence of an excess of unlabeled PGE<sub>2</sub>. The dissociation constant (K<sub>i</sub>) was then determined, and (Ia) produced a K<sub>i</sub> of 0.0002 µM for EP4 receptor subtypes.

**Chemistry:** 3,7-Dithiaprostanoid acid derivatives of formula (I) and their salts and cyclodextrin clathrates are new.

R1 = OH, 1-4C alkoxy or NR6R7; R6, R7 = independently H or 1-4C alkyl; R2 = H or OH; R3 = optionally substituted 1-8C alkyl, optionally substituted 2-8C alkenyl, optionally substituted 2-8C alkynyl, Ph or 3-7C cycloalkyl; a = double or single bond; the derivative may include the 8-epi equilibrium compound; provisos are given.

Several compounds are specifically claimed e.g. 11α,15α-dihydroxy-9-oxo-16β-methyl-3,7-dithiaprost-13E-enoic acid (Ia) (Example 2(o)).

39 pages

Drawings 0/0

**Authors:** Maruyama T; Ohuchida S

**Publication Date:** 29 July 1998

**Language:** English

**Priority:** 27 January 1997 JP-027198

**Location:** Osaka, Japan

**Document Number:** EP-855389-A2

**Filed:** 26 January 1998 as 300513

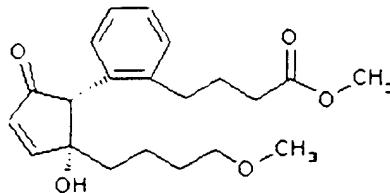
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WD-98-009700

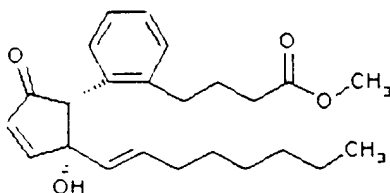
PP - Cardiovascular

[Front Page](#)**[April 16, 1999] New series of osteogenesis-promoting agents developed at Taisho**

Taisho scientists have prepared and evaluated two series of **phenyl-substituted hydroxycyclopentenone analogues with osteogenesis-promoting effects**. Compounds of the invention were found to significantly increase  $\text{Ca}^{2+}$  and alkaline phosphatase (ALP) in human long bone osteoblast cultures at a concentration of 5  $\mu\text{M}$  (JP 99043460 and JP 99043459).



JP 99043460



JP 99043459

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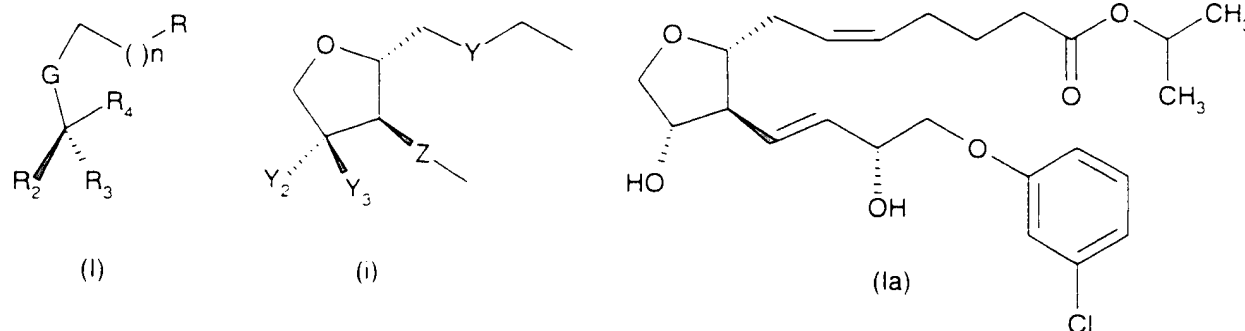


# Use of tetrahydrofuran prostaglandin analogs as prostaglandin/FP receptor agonists - for the treatment of glaucoma and ocular hypertension.

**Drug Activity:** Ophthalmological; Hypotensive

**Mechanism of Action:** Prostaglandin-Agonist

**Compound Name:** None Given



**Use:** For treating glaucoma and ocular hypertension (claimed). As agonists at the prostaglandin DP and FP receptors.

**Dosage:** 0.00003-0.5 (0.001-0.01) wt% solution for topical administration to the eye.

**Advantage:** Improved therapeutic profile compared to natural prostaglandins.

**Biological Data:** No data given.

**Chemistry:** The use of prostaglandin analogs of formula (I) for treating glaucoma or ocular hypertension is claimed.

R = an ester, CO<sub>2</sub>R<sub>1</sub>, CONR<sub>7</sub>R<sub>8</sub>, CH<sub>2</sub>OR<sub>9</sub> or CH<sub>2</sub>NR<sub>10</sub>R<sub>11</sub>; R<sub>1</sub> = H, or a cationic salt or ammonium moiety; R<sub>7</sub>, R<sub>8</sub> = independently H or alkyl; R<sub>9</sub> = H, acyl, or alkyl; R<sub>10</sub>, R<sub>11</sub> = independently H, acyl or alkyl (providing only one is acyl); n = 0 or 2; G = a group of formula (i) or two other defined tetrahydrofuran containing moieties; Y = CH<sub>2</sub>CH=CH (cis), CH=CHCH<sub>2</sub> (cis) or CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>; Z = CC, CH=CH (trans) or CH<sub>2</sub>CH<sub>2</sub>; one of Y<sub>2</sub>, Y<sub>3</sub> = H, and the other = F or OH (which may be modified); R<sub>4</sub> = cyclohexyl, 5-7C alkyl or R<sub>5</sub>; R<sub>5</sub> = (CH<sub>2</sub>)<sub>m</sub>Xphenyl or (CH<sub>2</sub>)<sub>p</sub>Z<sub>2</sub>; X = O or CH<sub>2</sub>; m = 1-6; phenyl is optionally substituted with halo, CH<sub>3</sub>, CF<sub>3</sub>, CN, OCH<sub>3</sub> or acetyl; p = 0-6; Z<sub>2</sub> = a defined optionally substituted bicyclic carbocycle or O-containing heterocycle; Several provisos are given.

(I) is e.g. isopropyl [2R(5Z),3S(1E,3R),4S]-7-[tetrahydro-3-{4-(3-chlorophenoxy)-3-hydroxy-1-butenyl]-4-hydroxy-2-furanyl]-5-heptenoate (Ia) (compound VI).

24 pages

Drawings 0/0

**Authors:** Selliah R D

**Publication Date:** 23 December 1998

**Language:** English

**Priority:** 18 June 1997 US-878030

**Location:** Fort Worth, Tex., USA

**Document Number:** WO9857942-A1

**Filed:** 03 June 1998 as U11339

**Designated States:** Regional: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE National: AU BR CA JP MX US

WD-99-000792

PP - Cardiovascular

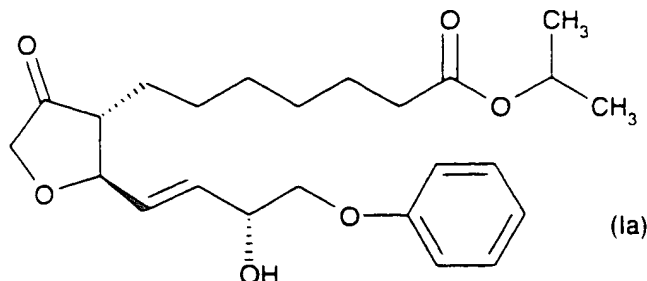
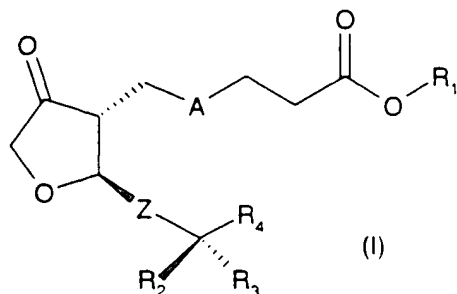
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# Use of tetrahydrofuran prostaglandin analogs as prostaglandin EP receptor agonists - for the treatment of glaucoma and ocular hypertension.

**Drug Activity:** Ophthalmological; Hypotensive

**Mechanism of Action:** Prostaglandin-Agonist

**Compound Name:** None Given



**Use:** For treating glaucoma or ocular hypertension (claimed). As agonists at the prostaglandin EP receptor.

**Dosage:** 0.00003-0.5 (0.001-0.01) wt% solution for topical administration to the eye.

**Advantage:** Improved therapeutic profile compared to natural prostaglandins.

**Biological Data:** No suitable data given.

**Chemistry:** The use of prostaglandin analogs of formula (I) for treating glaucoma or ocular hypertension is claimed.

R1 = H, 1-5C alkyl, 3-6C cycloalkyl or a cationic salt moiety; A = CH<sub>2</sub>CH=CH (cis), CH=CHCH<sub>2</sub> (cis) or CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>; Z = CC, CH=CH (trans) or CH<sub>2</sub>CH<sub>2</sub>; One of R<sub>2</sub>, R<sub>3</sub> = H, and the other = F or OH (which may be modified), or R<sub>2</sub> and R<sub>3</sub> together = OCH<sub>2</sub>CH<sub>2</sub>O, or carbonyl; R<sub>4</sub> = (CH<sub>2</sub>)<sub>m</sub>Xphenyl or (CH<sub>2</sub>)<sub>p</sub>Z<sub>2</sub>. X = O or CH<sub>2</sub>; m = 1-6; phenyl is optionally substituted with halo, CH<sub>3</sub>, CF<sub>3</sub>, CN, OCH<sub>3</sub> or acetyl. p = 0-6; Z<sub>2</sub> = a defined optionally substituted bicyclic carbocycle or O-containing heterocycle.

The use of isopropyl [2R(1E,3R)-7-[tetrahydro-2-(4-phenoxy-3-hydroxy-1-butenyl)-4-oxo-3-furanyl]heptanoate (Ia) (compound III) is specifically claimed.

23 pages

Drawings 0/0

**Authors:** Selliah R D

**Publication Date:** 23 December 1998

**Language:** English

**Priority:** 18 June 1997 US-878031

**Location:** Fort Worth, Tex., USA

**Document Number:** WO9857930-A1

**Filed:** 03 June 1998 as U11340

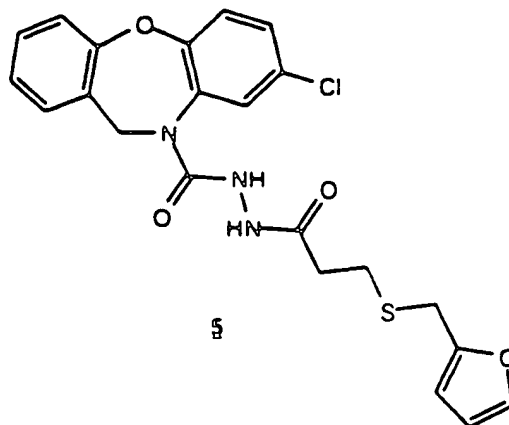
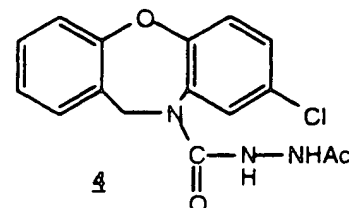
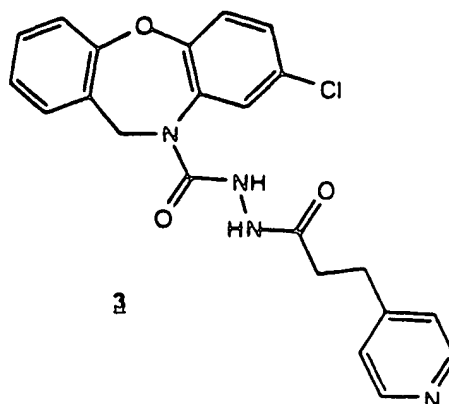
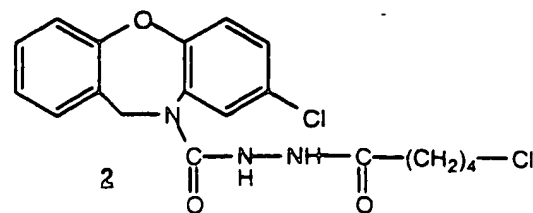
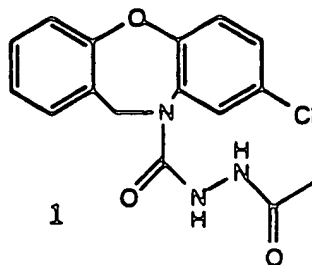
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EP  
antagonists



Recently, additional evidence for the involvement of  $\text{PGE}_2$  and hence EP receptor subtypes in inflammation and pain has been reported. Specific monoclonal antibodies to  $\text{PGE}_2$  (termed 2B5), that neutralize the activity of  $\text{PGE}_2$ , were efficacious in a phenylbenzoquinone-induced model of nociception (20). Furthermore, these antibodies could reverse established hyperalgesia in a carrageenan-induced hyperalgesia model (21). The 2B5 antibodies were also able to substantially reverse edema

formation in a rat adjuvant-induced arthritis model (21). Remarkably, the efficacy of 2B5 in these inflammatory models was indistinguishable from that of indomethacin, a potent NSAID. In the most recent study, 2B5 was shown to be as efficacious as the COX-2 selective inhibitor, SC-58635, in a carrageenan-induced hyperalgesia model in rat (22). It is clear from these as well as previous studies that blockade of EP subtype receptor(s) could conceivably be as efficacious as NSAIDs in the treatment of inflammatory diseases without any of the undesirable side-effects associated with them.

Gastric Antisecretory and Cytoprotective Agents - PGs, especially  $\text{PGE}_2$ , are known to have mucosal protective effects and act through a number of different mechanisms